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## Role of VEGF receptor-1 (Flt-1) in mediating calcium-dependent nitric oxide release and limiting DNA synthesis in human trophoblast cells.

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Vascular endothelial growth factor (VEGF) receptor KDR (kinase-insert-domain-containing receptor) is linked to endothelial cell proliferation, and VEGF receptor Flt-1 (fms-like tyrosine kinase) is essential for the organization of embryonic vasculature. Flt-1 is also known to be expressed on adult endothelial and trophoblast cells, although its function has not yet been established. Herein we report that human trophoblast and endothelial cells contain functional Flt-1 receptors for VEGF that trigger the synthesis and release of nitric oxide (NO) by the activation of constitutive NO synthase (cNOS). In first-trimester human trophoblast cells isolated by chorionic villous sampling, VEGF<sub>165</sub> stimulated NO release in a concentration- and time-dependent manner, with a maximal increase of 60% (in comparison to basal release levels) occurring within 30 minutes (basal: 1342 pmol/ml; VEGF (10 ng/ml): 2162 pmol/ml;  $p < 0.001$ ), as measured by an NO chemiluminescence analyzer. VEGF<sub>20</sub>, a peptide fragment that is composed of the first 20 amino acids at N-terminus, displayed properties of a partial agonist. VEGF<sub>165</sub>- and VEGF<sub>20</sub>-mediated NO biosynthesis was attenuated by NG-nitro-L-arginine in a concentration-dependent fashion, indicating NOS activation. VEGF-neutralizing anti-VEGF monoclonal antibody significantly inhibited VEGF-mediated NO release ( $p < 0.001$ ), and the addition of a neutralizing anti-Flt-1 antibody inhibited the response by 79.6%  $\pm$  7.59%, an effect found to be reversible with higher concentrations of VEGF. In contrast, anti-KDR antibody had no significant inhibitory effect. RT-PCR confirmed the presence of mRNA encoding the

Flt-1 and KDR receptors as well as the endothelial form of cNOS in trophoblast cells. VEGF165-stimulated NO release was inhibited by genistein (5 microM;  $p < 0.001$ ) as well as by the removal of calcium from the extracellular environment ( $p < 0.001$ ), which suggests the contingency of this process on tyrosine phosphorylation and extracellular calcium, respectively. Addition of sodium nitroprusside, an NO donor, inhibited trophoblast DNA synthesis in a concentration-dependent manner, as measured by [3H]thymidine incorporation, without affecting cell viability. VEGF under maximal NO production had no mitogenic activity, suggesting that trophoblast-derived NO may limit trophoblast proliferation. Endogenous trophoblast DNA synthesis increased 3-fold in the presence of anti-Flt-1 antibody but not in the presence of anti-KDR antibody, suggesting that Flt-1 functions as a growth suppressive receptor to counteract the proliferative actions of KDR. Levels of immunoreactive endothelial cNOS were markedly increased in growth-restricted placentae ( $n = 4$ ) in comparison to those of normal ( $n = 5$ ) placentae, which may account for the relatively small-sized placentae associated with intrauterine growth restriction. VEGF165 stimulated NO release via phosphorylation of the Flt-1 receptor, indicating that VEGF may be an autocrine regulator of NO biosynthesis by aiding trophoblast penetration into spiral arterioles during the first trimester and preventing platelet aggregation within the placenta. Finally, the activation of Flt-1 receptor suppressed trophoblast DNA synthesis within the placenta via NO.

MeSH Terms:

- Calcium/metabolism\*
- Cells, Cultured
- DNA/biosynthesis\*
- DNA Primers/chemistry
- Endothelial Growth Factors/pharmacology
- Endothelium, Vascular/cytology
- Endothelium, Vascular/drug effects
- Endothelium, Vascular/metabolism
- Epidermal Growth Factor/pharmacology
- Female
- Humans
- Immunoenzyme Techniques
- Lymphokines/pharmacology
- Nitric Oxide/metabolism\*
- Nitric-Oxide Synthase/metabolism
- Nitroprusside/pharmacology
- Polymerase Chain Reaction
- Pregnancy
- Proto-Oncogene Proteins/physiology\*
- Receptor Protein-Tyrosine Kinases/physiology\*
- Receptors, Growth Factor/physiology
- Research Support, Non-U.S. Gov't
- Trophoblasts/cytology
- Trophoblasts/drug effects
- Trophoblasts/metabolism\*
- Vascular Endothelial Growth Factor A

- [Vascular Endothelial Growth Factor Receptor-1](#)
- [Vascular Endothelial Growth Factors](#)

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- [Receptors, Growth Factor](#)
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